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(19)

(54) DERIVATIVES OF 17α-HYDROXY-ANDROST-4-ENE-17β-CARBOXYLIC ACIDS

(71) We, GLAXO LABORATORIES LIMITED, a British Company, of Greenford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with steroid compounds having anti-inflammatory properties.

Since the discovery of cortisone, a wide [illegible] of analogous structure on topical administration.

Anti-inflammatory steroids of the pregnane series so far described, being generally analogous to cortisone, tend to a greater or lesser extent to exert the physiological action of the natural hormone and thus possess, in addition to anti-inflammatory action, other actions similar to cortisone-like compounds. The physiological effects of the pregnane-type anti-inflammatory steroids may be broadly classified as glucocorticoid and mineralocorticoid effects, anti-inflammatory action at least until recently having been regarded as a glucocorticoid action. Glucocorticoid effects also include general disturbance of the body metabolism and may be very undesirable. Mineralocorticoid effects involve disturbance of the salt and water balance within the body and compounds having marked mineralocorticoid action are thus likely to produce undesirable effects on administration.

Even in the topical application of anti-inflammatory steroids, there is a risk that the steroid may be absorbed into the system through the skin, with subsequent development of undesired side effects.

There is thus a general desire to have available an anti-inflammatory steroid with high anti-inflammatory action but with which the undesired effects, either mineralocorticoid or glucocorticoid in nature, are reduced.

We have now found that certain new steroids of the androstane series possess marked anti-inflammatory action. Moreover our researches indicate that generally the ratio of anti-inflammatory action to undesired cortisone-like action in our new compounds is generally good.

These steroid compounds with which the [illegible] of the

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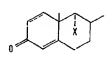
8th August, 1975



wherein a) X represents a hydrogen, chlorine or fluorine atom; R_1 represents a hydroxy group in the β-configuration or (when X represents a chlorine atom) R_1 may also represent a chlorine atom in the β-configuration; R_2 represents a hydrogen atom, a methylene group or a methyl group (in either the α- or β-configuration); R_3 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or a phenyl group; R_4 represents a C_{1-4} alkyl group; a C_{1-4} alkyl group substituted by either at least one halogen or an alkoxycarbonyl group wherein the alkoxy moiety contains 1 to 4 carbon atoms; or a (C_{2-4}) alkyl group substituted by a C_{2-4} alkanoyloxy group; and —— represents a single or double bond; provided that R_4 is not propyl, isopropyl or n-butyl unless one or more of X, R_2 and R_3 is other than hydrogen

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This invention is concerned with steroid compounds having anti-inflammatory properties.

Since the discovery of cortisone, a wide variety of compounds of analogous structure have been prepared having anti-inflammatory properties, such compounds being generally members of the pregnane series.

Anti-inflammatory steroids have found wide use in medicine and in latter years considerable attention has been directed to compounds having high anti-inflammatory action on topical administration.

Anti-inflammatory steroids of the pregnane series so far described, being generally analogous to cortisone, tend to a greater or lesser extent to exert the physiological action of the natural hormone and thus possess, in addition to anti-inflammatory action, other actions similar to cortisone-like compounds. The physiological effects of the pregnane-type anti-inflammatory steroids may be broadly classified as glucocorticoid and mineralocorticoid effects, anti-inflammatory action at least until recently having been regarded as a glucocorticoid action. Glucocorticoid effects also include general disturbance of the body metabolism and may be very undesirable. Mineralocorticoid effects involve disturbance of the salt and water balance within the body and compounds having marked mineralocorticoid action are thus likely to produce undesirable effects on administration.

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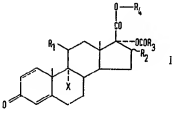
There is thus a general desire to have available an anti-inflammatory steroid with high anti-inflammatory action but with which the undesired effects, either mineralocorticoid or glucocorticoid in nature, are reduced.

We have now found that certain new steroids of the androstane series possess marked anti-inflammatory action. Moreover our researches indicate that generally the ratio of anti-inflammatory action to undesired cortisone-like action in our new compounds is generally good.

The steroid compounds with which the invention is concerned are compounds of the general formula



I

wherein a) X represents a hydrogen, chlorine or fluorine atom; R_1 represents a hydroxy group in the β-configuration or (when X represents a chlorine atom) R_1 may also represent a chlorine atom in the β-configuration; R_2 represents a hydrogen atom, a methylene group or a methyl group (in either the α- or β-configuration); R_3 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or a phenyl group; R_4 represents a C_{1-4} alkyl group; a C_{1-4} alkyl group substituted by either at least one halogen or an alkoxycarbonyl group wherein the alkoxy moiety contains 1 to 4 carbon atoms; or a (C_{2-4}) alkyl group substituted by a C_{2-4} alkanoyloxy group; and ——— represents a single or double bond; provided that R_1 is not propyl, isopropyl or n-butyl unless one or more of X, R_2 and R_3 is other than hydrogen

and/or ---- represents a double bond; or b) X represents a chlorine or fluorine atom; R_1 represents an oxo group; R_2 represents a hydrogen atom, a methylene group or a methyl group (in either the α- or β-configuration); R_3 represents a methyl or ethyl group; R_4 represents a C_{2-4} alkyl group; a C_{1-4} alkyl group substituted by either at least one halogen atom or an alkoxycarbonyl group wherein the alkoxy moiety contains 1 to 4 carbon atoms; or a (C_{2-4}) alkyl group substituted by a C_{2-5} alkanoyloxy group; and ---- represents a single or double bond.

The new androstane compounds have anti-inflammatory action on topical and internal administration, the anti-inflammatory activity of the compounds on topical administration being generally high.

In general, the group R_3 in formula I is preferably an alkyl group containing up to 3 carbon atoms, i.e. a methyl, ethyl, n-propyl or iso-propyl group. In compounds wherein R_3 represents a hydrogen atom R_4 preferably represents a methyl group.

The group R_4 in formula I is preferably a methyl, ethyl or propyl group.

In regard to the possible substituents of the lower alkyl group, the halogen atom is preferably a fluorine, chlorine or bromine atom, the C_{2-5} alkanoyloxy group is preferably an acetoxy group and the alkoxycarbonyl group is advantageously a methoxycarbonyl group.

Generally compounds of formula I in which R_1 represents a β-hydroxy group are preferred. Also in general terms, compounds of formula I in which R_2 represents a methyl group in the β-configuration are preferred on account of their high topical anti-inflammatory activity.

A preferred class of compounds of formula I having particularly good topical anti-inflammatory activity with a favourable ratio of topical anti-inflammatory activity to glucocorticoid activity are those compounds wherein X represents a chlorine or fluorine atom (preferably a fluorine atom), R_1 represents a β-hydroxy group, R_2 represents a methyl group (preferably in the β-configuration), R_3 represents a methyl, ethyl or n-propyl group, R_4 represents a methyl group and ---- represents a double bond. A further preferred class of compounds of formula I also having good topical anti-inflammatory activity with a favourable ratio of topical anti-inflammatory activity to glucocorticoid activity are those wherein X represents a fluorine or chlorine atom (preferably a fluorine atom), R_1 represents a keto group, R_2 represents a methyl group in the β-configuration, R_3 represents a methyl or ethyl group, R_4 represents a methyl group and ---- represents a double bond.

Yet another preferred class of compounds of formula I having high topical anti-inflammatory activity are those wherein X represents a fluorine or chlorine atom (preferably a fluorine atom), R_1 represents a β-hydroxy group, R_2 represents a methylene group, R_3 represents a methyl, ethyl n-propyl or iso-propyl group, R_4 represents a methyl or ethyl group (preferably a methyl group) and ---- preferably represents a double bond.

A preferred class of Δ^1 compounds of formula I (i.e. compounds wherein ---- represents a single bond) having especially good topical anti-inflammatory activity and ratio of topical anti-inflammatory activity to glucocorticoid activity are those wherein X represents a fluorine or chlorine atom (preferably a fluorine atom), R_1 represents a β-hydroxy group, R_2 represents a methyl group (preferably in the β-configuration), R_3 represents a methyl, ethyl or n-propyl group and R_4 represents a methyl or ethyl group (preferably a methyl group).

A still further class of compounds of formula I having good topical anti-inflammatory activity are those wherein X represents a hydrogen atom, R_1 represents a β-hydroxy group and R_2 preferably represents a hydrogen atom or a methyl group (especially in the β-configuration), R_3 preferably represents an alkyl group containing 1, 2 or 3 carbon atoms, particularly one containing 2 carbon atoms, R_4 preferably represents a lower alkyl group (e.g. a methyl group) and ---- preferably represents a double bond. Indeed, those compounds of this class wherein R_2 represents a methyl group in the β-configuration have been found to possess especially high topical anti-inflammatory activity.

Yet another class of compounds of formula I having good topical anti-inflammatory activity and a good ratio of topical anti-inflammatory activity to glucocorticoid activity are those wherein X and R_1 represent chlorine atoms, R_2 represents a methyl group preferably in the α-configuration, R_3 represents a methyl or ethyl group, R_4 represents a methyl or ethyl group and ---- preferably represents a double bond.

Individual preferred androstanes which have been found to have especially good topical anti-inflammatory activity with generally low levels of glucocorticoid activity include:

methyl 17α - acetoxy - 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxoandrosta-1,4-diene-17β-carboxylate

methyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate

methyl 17α - butyryloxy - 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxoandrosta-1,4-diene-17β-carboxylate

methyl 17α - acetoxy - 9α - fluoro - 11β-hydroxy - 16α - methyl - 3 - oxoandrosta-1,4-diene-17β-carboxylate

methyl 9α - fluoro - 11β - hydroxy - 16α-methyl - 3 - oxo - 17α - propionyloxy-

androsta - 1,4 - diene - 17β - carboxylate
methyl 17α - butyryloxy - 9α - fluoro - 11β-hydroxy - 16α - methyl - 3 - oxoandrosta-1,4-diene-17β-carboxylate
methyl 9α - fluoro - 11β - hydroxy - 16-methylene - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate
methyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxy-androst-4-ene-17β-carboxylate
methyl 17α - acetoxy - 9α - fluoro - 16β-methyl - 3,11 - dioxoandrosta - 1,4 - diene-17β-carboxylate
ethyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxy-androsta-1,4-dine-17β-carboxylate
methyl 17α - acetoxy - 9α,11β - dichloro-16α - methyl - 3 - oxo - androsta - 1,4-diene - 17β - carboxylate
methyl 9α - fluoro - 11β - hydroxy - 17α-isobutyryloxy - 16 - methylene - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate
ethyl 9α - fluoro - 11β - hydroxy - 17α-isobutyryloxy - 16 - methylene - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate and
methyl 11β - hydroxy - 16β - methyl - 3 - oxo-17α - propionyloxyandrosta - 1,4 - diene-17β-carboxylate.

The invention further includes the compound 2' - hydroxyethyl - 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxyandrosta - 1,4 - diene - 17β-carboxylate which is useful as an intermediate for the preparation of the corresponding halogen substituted alkyl derivatives and moreover has topical anti-inflammatory activity.

There are also provided pharmaceutical compositions for use in anti-inflammatory therapy, comprising at least one androstane compound of formula I (as defined above), together with one or more pharmaceutical carriers or excipients. Such compositions may be in forms adapted for topical or internal administration.

The active androstane compounds may be formulated into a preparation suitable for topical administration with the aid of a topical vehicle therefor. Examples of various types of preparation for topical administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butane-diol. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, colouring agents and perfumes.

Powders may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilising agents.

Spray compositions may for example be formulated as aerosols with the use of a suitable propellant, e.g. dichlorodifluoromethane or trichlorofluoromethane.

The proportion of active androstane compound in the topical compositions according to the invention depends on the precise type of formulations to be prepared but will generally be within the range of from 0.0001 to 5.0% by weight. Generally however for most types of preparations advantageously the proportion used will be within the range of from 0.001 to 0.5% and preferably 0.01 to 0.25%.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may often be used with advantage.

For internal administration the new compounds according to the invention, may for example, be formulated for oral, parenteral or rectal administration. For oral administration, syrups, elixirs, powders and granules may be used which may be formulated in conventional manner. Dosage unit forms are however preferred as described below.

For parenteral administration the compounds may be presented in sterile aqueous or oily vehicles, suitable oily vehicles including arachis oil and olive oil.

Preferred forms of preparation for internal administration are dosage unit forms i.e. presentations in unitary form in which each unit contains a desired dose of the active steroid. Such dosage unit forms contain from 0.05 to 2.0 mg, preferably from 0.25 to 1.0 mg, of the active steroid. For oral administration suitable dosage unit forms include tablets, coated tablets and capsules. For parenteral administration dosage unit forms include sealed ampoules or vials each containing a desired dose of the steroid. Suppositories, which may be prepared for example with conventional commercial suppository bases, provide a dosage unit form for rectal administration. Sterile tablet or pellet implants may also be used, e.g. where slow systemic absorption is desired.

The compounds according to the invention may in general be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

In general terms preparations for internal administration may contain from 0.01 to 5.0% of active ingredient dependent upon the type of preparation involved. The daily dose may vary from 0.05 to 10.0 mg. dependent on the condition being treated and the duration of treatment desired.

The compositions according to the invention may also include one or more preservatives or bacteriostatic agents e.g. methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol or benzalkonium chlorides. The compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics, such as neomycin.

The compounds of formula I (as defined above) may be generally prepared by esterifying a corresponding 17α - monoester 17β-carboxylic acid (or functional equivalent thereof) or 17α - hydroxy 17β - carboxylate to produce the desired compound of formula I.

As is well known to those skilled in the art it may frequently be convenient to elaborate the desired substituents in the 17α- and 17β-positions at an intermediate stage of the preparation of the desired final compound, one or more other substituents (or unsaturation) being introduced at a later stage. For example, it is possible for the preparation of 11-oxo compounds first to prepare an 11β-hydroxy compound having the desired 17α-acyloxy group and the desired 17β-carboxylate ester group and then oxidise the 11β-hydroxy group. Other instances where the desired substituents may be introduced before final elaboration of the remainder of the desired androstane molecule include for example preparing $\Delta^{9(11)}$ or Ring A saturated compounds having the desired 17α-acyloxy and 17β-carboxylate ester groups, completion of the elaboration of Rings A, B and C then being completed in conventional manner.

The elaboration of the characteristic 17-substituents of our new androstane compounds may be conveniently effected from pregnane compounds (having the following partial formula at the 17-position:

by an oxidation in known manner to form a corresponding androstane 17β-carboxylic acid which acid may then be esterified. The 17α-hydroxy group may be esterified or otherwise functionally converted prior to oxidation, and thereafter regenerated or converted, if desired, to a different 17α-acyloxy group.

The oxidative removal of the 21-carbon atom of the pregnane starting material may be effected for example with periodic acid, preferably in a solvent medium and preferably at room temperature. Alternatively, sodium bismuthate may be employed to effect the desired oxidative removal of the 21-carbon atom of a 17α-acyloxy pregnane compound.

As will be appreciated, should the starting pregnane compound contain any substituent sensitive to the above-described oxidation such group should be suitably protected.

The parent 17β-carboxylic acids of compounds of formula I may be esterified in known manner to provide 17β-carboxylate esters according to the invention. For example, in order to prepare a lower alkyl ester the 17β-carboxylic acid may be reacted with an appropriate diazoalkane, e.g. diazomethane, the reaction being preferably effected in a solvent medium, e.g. ether, tetrahydrofuran or methanol, and at a low temperature, preferably at -5 to $+30$°C. Alternatively, the 17β-carboxylic acid may be reacted with an appropriate O-alkyl-N,N^1-dicyclohexyl-isourea e.g. O - t - butyl - N,N^1 - dicyclohexyl - isourea, preferably in an aprotic solvent such as ethyl acetate, and advantageously at a temperature of 25—100°C. Alternatively, a salt of the parent 17β-carboxylic acid, for example, an alkali metal e.g. lithium, sodium or potassium, salt or a quaternary ammonium, e.g. triethyl ammonium or tetrabutyl ammonium, salt may be reacted with an appropriate alkylating agent, for example, an alkyl halide e.g. the iodide or a dialkyl sulphate e.g. dimethylsulphate, preferably in a polar solvent medium such as acetone, methylethyl ketone or dimethyl formamide, conveniently at a temperature in the range 25—100°C. The reaction with an alkyl halide may conveniently be employed to prepare the ethyl and propyl 17β-carboxylate esters and higher alkyl esters according to the present invention.

Alternatively, the parent 17α-hydroxy-17β-carboxylic acids of the compounds of formula I may be esterified in known manner to provide the corresponding 17α - hydroxy - 17β-carboxylate esters. For example, the 17β-carboxylic acid may be reacted with a diazoalkane or an O-alkyl-dicyclohexyl-isourea, or a salt of the 17β-carboxylic acid may be reacted with an alkylating agent as described above for the preparation of the 17β-carboxylate esters of the invention. The 17α-hydroxy-17β-carboxylate esters may then be further esterified in known manner to produce the compounds of the invention.

The esterification of the 17α-hydroxy group in the above-described preparation of the new androstane compounds may be effected in known manner, e.g. by reacting the parent 17α-hydroxy compound with an appropriate

carboxylic acid, advantageously in the presence of trifluoroacetic anhydride and preferably in the presence of an acid catalyst, e.g. *p*-toluenesulphonic acid or sulphosalicylic acid.

The reaction is advantageously effected in an organic solvent medium such as benzene, methylene chloride or an excess of the carboxylic acid employed, the reaction being conveniently effected at a temperature of 20—100°C.

Alternatively, the 17α-hydroxy group may be esterified by reaction of the parent 17α-hydroxy compound with the appropriate acid anhydride or acid chloride, if desired, in the presence of non-hydroxylic solvents, e.g. chloroform, methylene chloride or benzene, and preferably in the presence of a strong acid catalyst, e.g. perchloric acid, *p*-toluene sulphonic acid or a strongly acidic cation exchange resin, e.g. Amberlite IR 120 (the word "Amberlite" is a registered Trade Mark), the reaction being conveniently effected at a temperature of 25 to 100°C.

For the preparation of the 17α-esters of the 17β-carboxylic acids which may be employed in the preparation of the compounds according to the invention, it is often preferred to treat the parent 17α-hydroxy compound with the appropriate carboxylic acid anhydride to give the 17α-ester of the mixed anhydride of the androstane 17β-carboxylic acid and the carboxylic acid of the starting anhydride, this reaction being conveniently effected at an elevated temperature, the resulting anhydride then being solvolysed under acidic conditions (e.g. using aqueous acetic acid) or under basic conditions (e.g. using aqueous pyridine or a secondary amine such as diethylamine in acetone).

Alternatively, the parent 17α-hydroxy compound may be treated with the appropriate carboxylic acid chloride, preferably in a solvent such as an halogenated hydrocarbon e.g. methylene chloride, and advantageously in the presence of a base such as triethylamine, preferably at a low temperature e.g. 0°C.

Compounds wherein the 11-position contains a keto group may be prepared for example by oxidation of a corresponding 11β-hydroxy compound, e.g. by means of chromium trioxide, conveniently in an inert solvent such as acetone, preferably in the presence of sulphuric acid. Alternatively, chromium trioxide in the presence of pyridine may be employed.

The above-described oxidation of an 11β-hydroxy group into an 11-keto group may be effected at any convenient stage in the synthesis of the androstane compounds, e.g. prior to or after the oxidative removal of the 21-carbon atom of the above-mentioned pregnane starting material or the esterification of the 17α-hydroxy group.

Those compounds of formula I (wherein R_1 represents a C_{1-4} alkyl group substituted by either at least one halogen atom or a C_{2-5} alkoxycarbonyl group; or a C_{2-4} alkyl group substituted by a C_{2-5} alkanoyloxy group) may be prepared for example by reacting a salt of the parent 17β-carboxylic acid with an appropriate halo compound serving to introduce the desired group R_1 in the compound of formula I.

This reaction is advantageously effected using as the salt of the parent 17β-carboxylic acid an alkali metal e.g. lithium, sodium or potassium, salt or a quaternary ammonium salt such as the triethylammonium or tetrabutylammonium salt, conveniently in a polar solvent such as acetone, methylethyl ketone or dimethyl formamide.

If desired, the substituted lower alkyl groups represented by R_1 in formula I may be suitably modified in conventional manner.

Thus, in the case when R_1 in formula I represents an alkyl group substituted by a lower alkoxy-carbonyl group, the resulting compound may, if desired, be converted into a compound wherein R_1 represents an alkyl group with a different alkoxycarbonyl substituent by ester exchange e.g. by treatment with methanol in the presence of an acid catalyst such as perchloric acid to convert an ethoxycarbonyl compound into the corresponding methoxy-carbonyl compound.

In addition, the above-identified reaction of the salt of a 17β-carboxylic acid with a halo compound may be used to prepare compounds of the type of formula I wherein R_1 represents a C_{2-4} alkyl group substituted by a hydroxy group (in other than the α-position) which compounds may be converted into the corresponding halogen-substituted compounds via the corresponding sulphonyloxyalkyl e.g. mesyloxyalkyl, derivatives, such conversion being carried out in conventional manner.

Thus, the sulphonyloxyalkyl compound may be advantageously reacted with an alkali metal, alkaline earth metal or quaternary ammonium halide, preferably lithium chloride, conveniently in a solvent medium comprising, for example, acetone, dimethyl formamide or ethanol.

Alternatively, the above-mentioned hydroxyalkyl derivatives may be acylated e.g. with an appropriate carboxylic acid chloride or anhydride to produce compounds of formula I according to the invention wherein R_1 represents a C_{2-4} alkyl group substituted by a C_{2-5} alkanoyloxy group.

Compounds of formula I wherein R_1 represents a lower alkyl group substituted by a halogen atom at the carbon atom attached to the oxygen atom of the 17β-carboxylate may be prepared for example by reacting the parent 17β-carboxylic acid with an appropriate aldehyde in the presence of a hydrohalic acid. The reaction may advantageously be effected in the presence of a catalyst, for example zinc chloride.

The Δ^4 compounds according to the invention can conveniently be prepared by partial reduction of the corresponding $\Delta^{1,4}$ compound, for example, by hydrogenation using a palladium catalyst, conveniently in a solvent, e.g. ethyl acetate or by homogeneous hydrogenation using for example tris(triphenyl phosphine) rhodium chloride, conveniently in a solvent such as benzene, or by exchange hydrogenation using for example cyclohexene in the presence of a palladium catalyst in a solvent e.g. ethanol, preferably under reflux.

It is to be noted that androstane compounds corresponding to our new class of 17α-acyloxy compounds of the androstane series of formula I but characterised by a free hydroxy group at position 17 in the α configuration are new compounds apart from those compounds wherein X and R_3 are both hydrogen, R_1 is a C_{1-4} alkyl group, $\overset{\cdots}{\underset{\cdots}{\quad}}$ is a single bond and R_1 is a β-hydroxy group. Particularly preferred compounds are those wherein R_2 represents a methyl or methylene group and also those wherein X represents a chlorine or fluorine atom. Such new compounds are useful intermediates for the preparation of our new 17α-acyloxy compounds and constitute a further feature of the invention.

Other novel androstane compounds of use as intermediates in the preparation of the compounds of general formula I include the parent 17β-carboxylic acids of such compounds and their anhydrides, e.g. their mixed anhydrides with lower alkanoic acids, especially lower alkanoic acids such as acetic and propionic acids. Such 17β-carboxylic acids and their anhydrides also constitute further features of the present invention.

For a better understanding of the invention, the following Examples are given by way of illustration only, Examples 1, 17, 23, 34, 50, 53, 56 and 60 illustrating the preparation of starting materials which may be employed in the preparation of compounds according to the invention.

In the following Examples Nos. 1—37, the preparation of the compounds is described by reference to the following general methods of preparation A to F given below, details of the compound prepared in each case and its physical constants being given in the subsequent Tables. The references in Methods A to F to "parts w/v" in relation to the amounts of various materials, are intended to indicate the number of mls of material employed per gram of steroid.

Method A

Preparation of androstane - 17β - carboxylic acids.

A solution of the 20-keto-21-hydroxy pregnane steroid (1 part) in methanol (50 parts w/v) was treated with a solution of periodic acid (1.5 parts w/w) in water (10 parts w/v) at room temperature until the reaction was judged complete (thin-layer chromatography). Most of the methanol was evaporated and after addition of water the solid steroid 17β-carboxylic acid was removed by filtration and purified by crystallization.

Method B

Methylation of androstane 17β-carboxylic acids.

The androstane 17β-carboxylic acid (1 part) was dissolved in methanol (62—75 parts w/v) and treated at 0°C with an ethereal solution of diazomethane until a yellow colour persisted and the reaction was shown to be complete by thin-layer chromatography. After destruction of the excess diazomethane with a few drops of acetic acid the reaction mixture was evaporated to dryness *in vacuo* and the residue purified by crystallization.

Method C

Ethylation and propylation of androstane-17β-carboxylic acids.

The androstane - 17β - carboxylic acid (1 part) in acetone (100 parts w/v) was treated with triethylamine (1.2—5.0 equivalents based on the steroid) and then ethyl or propyl iodide (5 equivalents based upon the steroid). The mixture was refluxed until thin-layer chromatography indicated that the reaction was complete. Most of the solvent was removed *in vacuo* and the residue diluted with water to afford the product which was removed by filtration and purified by crystallization.

Preparation of C—17 esters by acylation of 17α - hydroxyandrostane - 17β - carboxylates.

Method D

The 17α-hydroxy-17-β-carboxylate (1 part) was mixed with the appropriate aliphatic carboxylic acid (10 parts w/v), trifluoroacetic anhydride (1—2.4 part w/v) and toluene-*p*-sulphonic acid (0.005—0.03 parts w/w added as an anhydrous solution in chloroform) and the mixture heated in an oil bath at 80°C until the reaction was judged, by thin-layer chromatography, to be complete. The cooled reaction mixture was poured into excess dilute sodium bicarbonate solution and stirred until all the excess anhydride had been decomposed. The precipitated product was removed by filtration and purified by crystallization.

Method E

The 17α - hydroxy - 17β - carboxylate (1 part) in the appropriate aliphatic carboxylic acid (about 20 parts w/v) was treated with trifluoracetic anhydride (5 parts w/v) and toluene-*p*-sulphonic acid (about 6 mg. as an anhydrous solution in chloroform) and the mixture kept at room temperature until the reaction was judged complete (t.l.c.). The mixture was poured into dilute sodium bicarbonate solution and the precipitated pro-

duct was removed by filtration, dried and recrystallized.

Method F

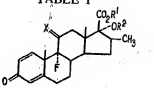
Oxidation of 11β-hydroxy steroids to 11-ketones.

The 11β-hydroxy steroid (1 part) was dissolved in acetone (25—150 parts w/v), cooled in an ice-bath and a solution of chromium trioxide (prepared by adding concentrated sulphuric acid (53.3 ml.) to chromium trioxide (66.7 g.) in water and making the volume up to 250 ml. by addition of water) (1.6—2.08 equivalents) was added. When the reaction was judged complete (t.l.c.) the mixture was diluted with ether or ether and ethyl acetate and washed thoroughly with water. Evaporation of the solvent afforded the crude 11-ketone which was purified by crystallization.

TABLE I

A=Acetone
P.E.=Petroleum-ether

General formula:



Example Nos. 1–16

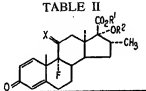
R^1	R^2	X	Method of Preparation	Cryst. Solvent	M.P. °C	$[\alpha]_D$ (Dioxan)	$\lambda_{max.}$ nm	ϵ	Empirical Formula	Found		Required	
										C	H	C	H
H	H	α-H; β-OH	A	A–P.E.	256–258	+62.5	238	15,200	$C_{31}H_{37}FO_5$	67.05	7.2	66.65	7.2
CH_3	H	α-H; β-OH	B	A–P.E.	241–243	+71.6	239	15,100	$C_{32}H_{39}FO_5$	67.3	7.5	67.35	7.45
C_2H_5	H	α-H; β-OH	C	A–P.E.	222–225	+68.6	238	15,200	$C_{33}H_{41}FO_5$	67.3	7.8	67.95	7.7
C_3H_7	H	α-H; β-OH	C	A–P.E.	191–193	+67.2	238	15,100	$C_{33}H_{39}FO_5$	68.2	8.0	68.55	7.9
CH_3	$COCH_3$	α-H; β-OH	D	A	233–235	+36.6	238	16,200	$C_{34}H_{41}FO_6$	66.6	7.0	66.35	7.2
CH_3	COC_2H_5	α-H; β-OH	D(1)	A–P.E.	232–235	+35.2	238	15,400	$C_{35}H_{43}FO_6$	66.9	7.2	66.95	7.4
CH_3	COC_3H_7	α-H; β-OH	D	A	235–236	+31.8	238	15,700	$C_{36}H_{45}FO_6$	67.7	7.5	67.5	7.6
C_2H_5	$COCH_3$	α-H; β-OH	D(2)	A–P.E.	255		238	15,100	$C_{34}H_{43}FO_6$	66.8	7.4	66.95	7.4
C_2H_5	COC_2H_5	α-H; β-OH	D(3)	A–P.E.	196	+34.2	238	15,300	$C_{35}H_{45}FO_6$	67.4	7.5	67.5	7.6
C_2H_5	COC_3H_7	α-H; β-OH	D(4)	A–P.E.	175–178	+35.5	238	15,100	$C_{36}H_{47}FO_6$	67.4	7.5	68.05	7.85
C_3H_7	$COCH_3$	α-H; β-OH	D(5)	A–P.E.	240–242		238	15,200	$C_{36}H_{47}FO_6$	67.25	7.6	67.5	7.6
C_3H_7	COC_2H_5	α-H; β-OH	D(6)	A–P.E.	178–180	+38.6	238	15,150	$C_{37}H_{49}FO_6$			68.05	7.85
C_3H_7	COC_3H_7	α-H; β-OH	D(7)	A–P.E.	175–177	+34.8	238	15,300	$C_{38}H_{51}FO_6$	68.6	8.0	68.55	8.0
CH_3	$COCH_3$	=O	F	A–P.E.	258–260	+78.6	235	15,800	$C_{34}H_{39}FO_6$	66.55	6.8	66.65	6.75
CH_3	COC_2H_5	=O	F	A–P.E.	228–230		235	15,600	$C_{35}H_{41}FO_6$	67.6	7.1	67.25	7.0
C_2H_5	COC_2H_5	=O	F	A–P.E.	183–185		235	14,700	$C_{36}H_{43}FO_6$	67.4	7.3	67.8	7.2

(1) The reaction mixture was partly evaporated *in vacuo* before dilution with sodium bicarbonate solution. The crude product was filtered through a short column of grade III neutral alumina in chloroform before crystallizing.
(2) A further quantity of trifluoracetic anhydride (0.5 parts w/v) was added to the reaction mixture.
(3) The crude product was extracted with ethyl acetate and purified by preparative thin-layer chromatography.
(4) No toluene- p-sulphonic acid was added to the reaction mixture which was heated to 65°.
(5) The crude product was purified by preparative thin-layer chromatography before crystallizing.
(6) No toluene-p-sulphonic acid was added to the reaction mixture.

TABLE II

A=Acetone
P.E.=Petroleum-ether

General formula:



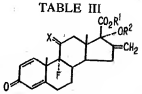
Example No.	R^1	R^2	X	Method of Preparation	Cryst. Solvent	M.P. °C	$[\alpha]_D$ (Dioxan)	$\lambda_{max.}$ nm	ϵ	Empirical Formula	Found		Required	
											C	H	C	H
17	H	H	α-H; β-OH	A	A–P.E.	Decomp. >258	+46.6	238	15,800	$C_{21}H_{27}PO_5$	66.6	7.25	66.65	7.2
18	CH_3	H	α-H; β-OH	B(1)	A–P.E.	271–273	+38.5	238	15,200	$C_{22}H_{29}FO_5$	67.0	7.3	67.35	7.45
19	CH_3	$COCH_3$	α-H; β-OH	D	A–P.E.	316–319	+11.5	238	15,700	$C_{24}H_{31}FO_6$	66.45	7.1	66.35	7.2
20	CH_3	COC_2H_5	α-H; β-OH	D(2)	A–P.E.	230–233	+15	238	15,000	$C_{25}H_{33}FO_6$	66.55	7.65	66.95	7.4
21	CH_3	COC_3H_7	α-H; β-OH	D(2)	A–P.E.	199–201	+14.3	238	14,700	$C_{26}H_{35}FO_6$	67.9	7.65	67.5	7.65
22	CH_3	COC_2H_5	=O	F	A–P.E.	185–188	+49.2	235	16,200	$C_{25}H_{31}FO_6$	67.1	6.9	67.25	7.0

(1) The crude product obtained by evaporation of the methanolic reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate and water before crystallization.
(2) The crude product was extracted with ethyl acetate and purified by preparative thin-layer chromatography.

TABLE III

A=Acetone
M=Methanol

General formula:



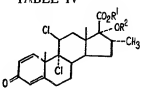
Example No.	R^1	R^2	X	Method of Preparation	Cryst. Solvent	M.P. °C	$[\alpha]_D$ (Dioxan)	$\lambda_{max.}$ nm	ϵ	Empirical Formula	Found		Required	
											C	H	C	H
23	H	H	α-H; β-OH	A	A	236–238	–23.4	238	15,500	$C_{21}H_{28}FO_5$	67.1	6.9	67.0	6.7
24	CH_3	H	α-H; β-OH	B	M	285–287	–24.5	238	15,000	$C_{22}H_{29}FO_5$	67.5	7.2	67.7	6.95
25	C_2H_5	H	α-H; β-OH	C	M	258–261	–23.2	238	15,410	$C_{13}H_{29}FO_5$	68.0	6.9	68.3	7.25
26	CH_3	$COCH_3$	α-H; β-OH	D(1)	M	254–258	–94.0	238	15,720	$C_{24}H_{31}FO_6$	66.5	6.9	66.65	6.75
27	CH_3	COC_2H_5	α-H; β-OH	D(2)	M	198–200	–97.5	238	15,200	$C_{25}H_{33}FO_6$	67.1	7.1	67.25	7.0
28	CH_3	COC_3H_7	α-H; β-OH	D(2)	M	189–192	–86.5	238	15,580	$C_{26}H_{33}FO_6$	67.4	7.4	67.8	7.2
29	CH_3	$COCH(CH_3)_2$	α-H; β-OH	D(3)	M	185–187	–84.0	238	15,580	$C_{26}H_{33}FO_6$	67.8	7.4	67.8	7.2
30	C_2H_5	$COCH_3$	α-H; β-OH	D	M	278–280	–99.0	238	15,300	$C_{25}H_{31}FO_6$	67.1	6.9	67.25	7.0
31	C_2H_5	COC_2H_5	α-H; β-OH	D(3)	M	195–197	–85.1	238	15,800	$C_{26}H_{33}FO_6$	67.7	7.2	67.8	7.2
32	C_2H_5	$COCH(CH_3)_2$	α-H; β-OH	D(2)	EtOAc	145–148	–79.5	238	15,600	$C_{27}H_{35}FO_6$	68.6	7.2	68.35	7.45
33	CH_3	$COCH_3$	=O	F	M	229–232	–42.7	235	15,390	$C_{24}H_{27}FO_6$	66.8	6.3	66.95	6.3

(1) The crude product was purified by preparative thin-layer chromatography before crystallizing.
(2) The crude product was extracted into ethyl acetate and purified by preparative thin-layer chromatography before crystallizing.
(3) The crude product was extracted with ethyl acetate.

TABLE IV

A=Acetone
P.E.=Petroleum-ether
H=Hexane

General formula:



Example No.	R^1	R^2	Method of Preparation	Cryst. Solvent	M.P. °C	$[\alpha]_D$ (Dioxan)	$\lambda_{max.}$ nm	ϵ	Empirical Formula	Found		Required	
										C	H	C	H
34	H	H	A(1)	A–EtOH–P.E.	264–266	+23.6	237	14,300	$C_{21}H_{28}Cl_2O_4$(2)	61.0	6.3	61.0	6.35
35	CH_3	H	B(3)	A–P.E.	248–251	+17.6	237	14,500	$C_{22}H_{28}Cl_2O_4$(4)	61.8	6.6	61.85	6.6
36	CH_3	$COCH_3$	E	A–H	253–255	+73.6	236	13,900	$C_{24}H_{30}Cl_2O_5$	61.2	6.4	61.4	6.45
37	CH_3	COC_2H_5	E	A–H	237–239	+73.0	236	14,100	$C_{25}H_{32}Cl_2O_5$	62.0	6.6	62.1	6.65

(1) 120 parts (w/v) of methanol was used and a little dioxan added to aid dissolution of the steroid.
(2) Found: Cl, 17.2. Required, Cl, 17.2%.
(3) The crude product from evaporation of the methanol was dissolved in chloroform and filtered through a short plug of neutral grade III alumina before crystallization.
(4) Found: Cl, 16.8. Required, Cl,16.6%.

Example 38.

Methyl 9α - fluoro - 11β,17α - dihydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene-17β-carboxylate.

Methyl iodide (12 ml.) was added to a solution of 9α - fluoro - 11β,17α - dihydroxy-16β - methyl - 3 - oxo - androsta - 1,4 - diene-17β-carboxylic acid (10.045 g.) in acetone (500 ml.) containing triethylamine (4.6 ml.) and the mixture refluxed, more methyl iodide (6 ml.) being added after 4 hours. After 5.25 hours most of the solvent was evaporated *in vacuo* and the residue diluted with sodium bicarbonate solution. The precipitated solid was removed by filtration and, after drying, was filtered through a short plug of grade (III) neutral alumina in ethyl acetate containing a little methanol. Evaporation of the eluate gave methyl 9α - fluoro - 11β,17α-dihydroxy - 16β - methyl - 3 - oxo - androsta-1,4-diene-17β-carboxylate with infrared and n.m.r. spectra resembling that of the methyl ester prepared with diazomethane.

Example 39.

17α - Acetoxy - 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene-17β - carboxylic acetic anhydride.

9α - Fluoro - 11β,17α - dihydroxy - 16β-methyl - 3 - oxoandrosta - 1,4 - diene - 17β-carboxylic acid (1 g.) was suspended in acetic anhydride (15 ml.) and heated on a steam-bath for 45 minutes and then at 115° for 1 hour by which time all the steroid had dissolved. The mixture was cooled and the precipitated material removed by filtration and recrystallized from acetone-hexane to afford 17α - acetoxy - 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene-17β - carboxylic acetic anhydride, m.p. 218—220° $[\alpha]_D$+42.4° (c 0.8, dioxan), $\lambda_{max.}$ 238 nm (ε 15,900) (Found: C, 64.65; H, 6.5. $C_{25}H_{31}FO_7$ requires C, 64.9; H, 6.75%).

Example 40.

17α - Acetoxy - 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene-17β - carboxylic acid.

(1) 17α - Acetoxy - 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxoandrosta-1,4 - diene - 17β - carboxylic acetic anhydride (530 mg.) was dissolved in acetic acid (100 ml.) and water (50 ml.) added and the mixture kept at room temperature until reaction was complete (45 minutes). Evaporation *in vacuo* afforded the product which, after crystallization from acetone-petroleum ether, gave 17α - acetoxy - 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene 17β - carboxylic acid, m.p. 212—214°, $[\alpha]_D$+22.2° (c 0.8, dioxan), $\lambda_{max.}$ 239 nm (ε 14,700) (Found: C, 64.1; H, 7.1. $C_{23}H_{31}FO_6$ requires C, 64.3; H, 7.05%).

(2) 17α - Acetoxy - 9α - fluoro - 11β - hydroxy - 16β - methyl - 3 -oxoandrosta - 1,4-diene - 17β - carboxylic acetic anhydride (57 mg.) was dissolved in 50% aqueous pyridine (8 ml.) and kept at room temperature for 45 minutes. Evaporation of the solvent gave a solid whose infrared and n.m.r. spectra were similar to those of the material prepared in (1) above.

Example 41.

9α - Fluoro - 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylic propionic anhydride.

9α - Fluoro - 11β,17α - dihydroxy - 16β-methyl - 3 - oxoandrosta - 1,4 - diene - 17β-carboxylic acid (1 g.) was suspended in propionic anhydride (15 ml.) and heated in an oil bath at 115° for 15 minutes during which time the steroid dissolved. The reaction mixture was diluted with petroleum ether (100 ml.) to afford a white crystalline solid which was removed by filtration and dried. Recrystallization from acetone-hexane gave 9α-fluoro - 11β - hydroxy - 16β - methyl - 3-oxo - 17α - propionyloxy - androsta - 1,4-diene - 17β - carboxylic propionic anhydride, m.p. 180—182°, $[\alpha]_D$+50.5° (c 0.7, dioxan), $\lambda_{max.}$ 238 nm (ε 15,700) (Found: C, 66.4; H, 7.1. $C_{27}H_{35}FO_7$ requires C, 66.1; H, 7.2%).

Example 42.

9α - Fluoro - 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylic acid.

(1) 9α - Fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylic propionic anhydride (342 mg.) was dissolved in acetic acid (25 ml.) and water (15 ml.) added and the mixture kept at room temperature until the reaction was judged complete (t.l.c.). Evaporation *in vacuo* of most of the solvent and dilution with water afforded the product which was recrystallized from acetone-hexane to give 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylic acid, m.p. 188—190° $\lambda_{max.}$ 239 nm (ε 15,600) (Found: C, 65.1; H, 7.5. $C_{24}H_{31}FO_6$. Me_2CO requires C, 65.8; H, 7.6%).

(2) 9α - Fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylic propionic anhydride (6.93 g.) in acetone (150 ml.) was treated with diethylamine (5 ml.) and the mixture kept at room temperature for about 0.5 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in water, acidified and extracted with ethyl acetate. The washed organic layer was evaporated *in vacuo* to give a solid which was triturated with ether to give 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylic acid.

Example 43.

Methyl 9α - fluoro - 16 - methylene - 3,11-dioxo - 17α - propionyloxyandrosta - 1,4-diene-17β-carboxylate.

Methyl 9α - fluoro - 11β - hydroxy - 16-methylene - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate (204 mg.) in acetone (4 ml.) was treated at room temperature with a solution of chromium trioxide (0.23 ml; prepared by adding concentrated sulphuric acid (53.3 ml.) to chromium trioxide (66.7 g.) in water and making the volume up to 250 ml with water). After 30 minutes the reaction mixture was diluted with ether and washed successively with water, sodium bicarbonate solution and water. The dried ethereal solution was evaporated *in vacuo* and the residue was recrystallized from methanol to afford the title compound, mp. 194—195°, $[\alpha]_D$ −37.8° (c 1.06, dioxan), $\lambda_{max.}$ 234.5 nm (ε 15,800), (Found: C, 67.3; H, 6.7. $C_{28}H_{29}FO_6$ requires C, 67.55; H, 6.58%).

Example 44.

Methyl - 17α - benzoyloxy - 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

A suspension of methyl 9α-fluoro-11β,17α-dihydroxy - 16β - methylandrosta - 1,4-diene - 17β - carboxylate (439 mg.) in methylene chloride (15 ml.) was treated with benzoic acid (573 mg.), trifluoroacetic anhydride (0.6 ml.) and toluene-*p*-sulphonic (12 mg.) and the mixture was stirred at 80°. After 48 hours the mixture was cooled and diluted with methylene chloride and the solution was washed with sodium bicarbonate and water. Evaporation of the dried organic solution afforded a residue which was purified by preparative thin layer chromatography and crystallisation from methanol to give the title benzoate m.p. 166—168°, $[\alpha]_D$+3.3° (*c* 1.09, dioxan). $\lambda_{max.}$ 232 nm (ε 27,800). (Found: C, 70.0; H, 6.6. $C_{29}H_{33}FO_6$ requires C, 70.14; H, 6.7%).

Example 45.

Methyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxy-androst - 4 - ene - 17β - carboxylate.

A solution of methyl 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxyandrosta - 1,4 - diene - 17β-carboxylate (454 mg.) in ethanol (45 ml) was treated with 5% palladium-charcoal (453 mg.) and cyclohexene (0.9 ml) and the mixture was refluxed for 15 minutes. Filtration of the cooled mixture and evaporation of the solvent *in vacuo* afforded a froth which, after purification by preparative thin layer chromatography and crystallisation from acetone-petroleum ether gave the title compound m.p. 204—208° $\lambda_{max.}$ 237.5 nm (ε 15,400) (Found: C, 66.8; H, 7.8. $C_{31}H_{35}FO_6$ requires C, 66.65; H, 7.8%).

Example 46.

Methyl 9α - fluoro - 16β - methyl - 3,11-dioxo - 17α - propionyloxyandrost - 4 - ene-17β-carboxylate.

A solution of methyl 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxyandrost - 4 - ene - 17β - carboxylate (100 mg) in acetone (7 ml) was treated, at 0°, with a solution of chromium trioxide [0.09 ml; prepared by adding concentrated sulphuric acid (53.3 ml.) to chromium trioxide (66.7 g.) in water and making the volume up to 250 ml with water]. After 1.25 hours the mixture was diluted with ether and ethyl acetate and washed thoroughly with water. Evaporation of the organic solvent then afforded a white solid which was crystallised from acetone-petroleum ether to give the title compound, m.p. 218—220° after previous softening, $\lambda_{max.}$ 234 nm (ε 16,000) (Found: C, 66.55; H, 7.4. $C_{32}H_{33}FO_6$ requires C, 66.95; H, 7.4%).

Example 47.

Methyl - 17α - acetoxy - 11β - hydroxy-3 - oxoandrosta - 1,4 - diene - 17β - carboxylate.

Periodic acid (14.163 g.) in water (80 ml) was added to a solution of prednisolone (8.286 g) in methanol (800 ml) and the resulting mixture was kept at room temperature. After 1 hour most of the methanol was evaporated *in vacuo*, the residue was diluted with water, and the crystalline 11β,17α-dihydroxy - 3 - oxoandrosta - 1,4 - diene-17β - carboxylic acid removed by filtration. The analytical sample which was crystallized from wet-acetone and petroleum ether had m.p. 264—266° (Found: C, 69.2; H, 7.4. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.5%).

The above carboxylic acid (3.6 g) in methanol (200 ml) was treated at 0° with an ethereal solution of diazomethane until the mixture was yellow. Evaporation of most of the organic solvent *in vacuo* and dilution of the residue with water afforded crystalline methyl 11β,17α - dihydroxy - 3 - oxoandrosta-1,4 - diene - 17β - carboxylate m.p. 203—206°. A sample crystallised from acetone-hexane had m.p. 202—205°, $[\alpha]_D$+59.6° (*c* 0.8 dioxan), $\lambda_{max.}$ 242 nm (ε 15,100) (Found: C, 70.0; H, 7.9. $C_{21}H_{28}O_5$ requires C, 69.98; H, 7.83%).

The above methyl ester (464 mg) in acetic acid (5 ml) was treated with trifluoroacetic anhydride (1 ml) and the mixture stirred at room temperature. After 1 hour toluene-*p*-sulphonic acid (7 mg) was added and the mixture kept at room temperature for a further 2.5 hours. Dilution of the solution with sodium bicarbonate solution afforded a precipitate which was removed by filtration and purified by preparative thin-layer chromatography and crystallization to yield the title compound m.p. 284—286°, $[\alpha]_D$+8.9° (*c* 0.7 dioxan), $\lambda_{max.}$ 243 nm (ε 15,000). (Found: C, 68.6; H, 7.6. $C_{22}H_{30}O_6$ requires C, 68.65; H, 7.5%).

Example 48.

Methyl 9α - fluoro - 11β,17α - dihydroxy-16β - methyl - 3 - oxoandrosta - 1,4 - diene-17β-carboxylate.

A solution of sodium 9α - fluoro - 11β,17α-dihydroxy - 16β - methyl - 3 - oxoandrosta-1,4 - diene - 17β - carboxylate (prepared by titration of a solution of 9α - fluoro - 11β,17α-dihydroxy - 16β - methyl - 3 - oxoandrosta-1,4 - diene - 17β - carboxylic acid (103 mg) in methanol (20 ml) with aqueous-methanolic N-sodium hydroxide solution to pH 8.3] was treated with methyl iodide (0.085 ml) and the mixture was refluxed. After 16 hours the solvent was evaporated *in vacuo*, the residue triturated with water and the insoluble material removed by filtration.

The n.m.r. spectrum of this material in $(CD_3)_2SO$ showed methyl signals at τ 6.36,

8.47, 8.84, and 8.92 due to the title compound.

Example 49.

2′ - Hydroxyethyl 9α - fluoro - 11β - hydroxy - 16β - methyl - 3 - oxo - 17α - propionyloxyandrosta - 1,4 - diene - 17β - carboxylate.

A solution of 9α - fluoro - 11β - hydroxy-16β - methyl 3 - oxo - 17α - propionyloxyandrosta - 1,4 - diene - 17β - carboxylic acid (200 mg.) in acetone (20 ml.) was treated with redistilled triethylamine (0.38 ml.) and 2-iodoethanol (0.36 ml.) and the mixture was refluxed for 20 hours when the reaction was judged to be complete (t.l.c.). Most of the solvent was removed *in vacuo* and water (45 ml). was added to give the product which was recrystallised. first from methanol then from acetone to give the title compound, m.p. 171—173°, $[\alpha]_D$+39.7° (*c* 0.99, dioxan), $\lambda_{max.}$ 237.5 nm (ε 15,650). (Found: C, 64.95; H, 7.2. $C_{26}H_{33}FO_7$ requires C, 65.3; H, 7.4%).

Example 50.

2′ - methanesulphonyloxyethyl 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxyandrosta - 1,4 - diene - 17β-carboxylate.

A solution of 2′ - hydroxyethyl 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxyandrosta - 1,4 - diene - 17β-carboxylate (240 mg.) in dry pyridine (1 ml.) was treated dropwise at −1° to −10° with redistilled methanesulphonyl chloride (0.2 ml.) After 40 minutes the mixture was poured into 2N-sulphuric acid (8 ml.) and triturated to give a solid which was purified by preparative thin-layer chromatography and recrystallisation from methanol to give the title compound m.p. 129—131°, $\lambda_{max.}$ 238 nm (ε 15,850) (Found: C, 58.5; H, 6.7. $C_{27}H_{37}FO_9S$ requires C, 58.3; H, 6.7%).

Example 51.

2′ - Chloroethyl 9α - fluoro - 11β - hydroxy - 16β - methyl - 3 - oxo - 17α - propionyloxyandrosta - 1,4 - diene - 17β - carboxylate.

A mixture of 2′ - methanesulphonyloxyethyl 9α - fluoro - 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylate (223 mg.) and dry lithium chloride (170 mg.) in acetone (9 ml.) was refluxed for 22 hours. After removal of solvent *in vacuo* the residue was triturated with water to give a solid which was purified by preparative thin-layer chormatography and crystallisation from ether to afford the title chloroethyl ester, m.p. 194—196°, $[\alpha]_D$+43.4° (*c* 0.99, dioxan), $\lambda_{max.}$ 237 nm (ε 15,800). (Found: C, 62.9: H, 6.9; Cl, 7.0. $C_{30}H_{34}ClFO_6$ requires C, 62.8; H, 6.9; Cl, 7.1%).

Example 52.

2′ - Bromoethyl 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxyandrosta - 1,4 - diene - 17β - carboxylate.

Treatment of 2′ - methanesulphonyloxyethyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylate (222 mg.) with dry lithium bromide (348 mg.) in acetone (9 ml.) for 2 hours followed by work-up as described in E. ample 52, with purification from ether, afforded the title bromoethyl ester, m.p. 182—184.5°, softening above 122°, $[\alpha]_D$+38.8° (*c* 1.02, dioxan), $\lambda_{max.}$ 237.5 nm (ε 16,000). (Found: C, 57.9; H, 6.3; Br, 14.6. $C_{26}H_{34}BrFO_6$ requires C, 57.7; H, 6.3; Br, 14.8%).

Example 53.

9α - Chloro - 11β,17α - dihydroxy - 16β-methyl - 3 - oxoandrosta - 1,4 - diene - 17β-carboxylic acid.

Treatment of 9α - chloro - 11β,17α,21-trihydroxy - 16β - methylpregna - 1,4 - diene-3,20 dione by the procedure described in Method A afforded, after recrystallisation from acetone-ethanol-petrol the title carboxylic acid, m.p. 247—249°, $[\alpha]_D$+93.0° (*c* 0.7 dioxan), $\lambda_{max.}$ 238.5 nm (ε 14,300). (Found: C, 63.3 H, 7.1. $C_{21}H_{27}ClO_4$ requires C, 63.85, H, 6.9%).

Example 54.

9α - Chloro - 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylic acid.

A mixture of 9α - chloro - 11β,17α - dihydroxy - 16β - methyl - 3 - oxoandrosta-1,4 - diene - 17β - carboxylic acid (1.42 g.) and triethylamine (1.66 ml.) in dry methylene chloride (35 ml.) was stirred at 0° and treated dropwise with propionyl chloride (1.32 ml). After 35 minutes at 0° the solution was diluted with methylene chloride, washed successively with 3% sodium bicarbonate solution, *N*-hydrochloric acid and water; after being dried (magnesium sulphate) solvent was removed *in vacuo* to give a colourless crystalline solid. This solid was dissolved in acetone (40 ml.) and treated with redistilled diethylamine (1.5 ml.); concentration *in vacuo* gave the crystalline diethylamine salt which was collected, dried, dissolved in water and the solution was acidified with 2N-hydrochloric acid. The product was extracted with ethyl acetate and solvent was removed to give crystalline 9α - chloro - 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylic acid (1.49 g.) m.p. 187—188° (decomp.) $[\alpha]_D$+52.0° (*c* 0.95, dioxan), $\lambda_{max.}$ 238 nm (E $\frac{1\%}{1cm.}$ 315).

Example 55.

Methyl 9α - chloro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylate.

A solution of 9α - chloro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylic acid (501 mg.) in acetone (20 ml.) was cooled in ice and treated with an ethereal solution of diazomethane according to Method B. After being subjected to chromatography on silica the product was recrystallised from methanol to give the title methyl ester, m.p. 214—217° (decomp.) $[\alpha]_D$+60.3° (*c* 0.97, dioxan), $\lambda_{max.}$ 237 nm (ε 15,700). (Found: C, 64.5; H, 7.2; Cl, 7.5. $C_{26}H_{33}ClO_6$ requires C, 64.6; H, 7.15; Cl, 7.6%).

Example 56.

11β,17α - Dihydroxy - 16β - methyl - 3-oxoandrosta - 1,4 - diene - 17β - carboxylic acid.

A solution of 11β,17α,21 - trihydroxy - 16β-methylpregna - 1,4 - diene - 3,20 - dione (640 mg.) in dioxan (28 ml.) was stirred and treated with a solution of periodic acid (1.76 g.) in water (14 ml.). After 40 minutes the solution was diluted with water (14 ml.) and concentrated *in vacuo*. The crystalline product (579 mg.) was recrystallised from acetone to give the title acid, m.p. 226—229° (decomp.), $[\alpha]_D$+78.0° (*c* 0.50, dimethylsulphoxide), $\lambda_{max.}$ 242 nm (ε 14,850), (Found: C, 70.1; H, 8.0. $C_{23}H_{32}O_5$ requires C, 70.0; H, 7.8%).

Example 57.

11β - Hydroxy - 16β - methyl - 3 - oxo-17α - propionyloxyandrosta - 1,4 - diene - 17β-carboxylic acid.

Treatment of 11β,17α - dihydroxy - 16β-methyl - 3 - oxoandrosta - 1,4 - diene - 17β-carboxylic acid (310 mg.) with propionyl chloride (0.269 ml.) followed by solvolysis of the resulting product with diethylamine by the method described in Example 55 afforded crystalline 11β - hydroxy - 16β - methyl - 3-oxo - 17α - propionyloxyandrosta - 1,4 - diene-17β-carboxylic acid, m.p. 202—205° (decomp.), $[\alpha]_D$+24.4° (*c* 0.97, dioxan), $\lambda_{max.}$ 242.5 nm (ε 14,820).

Example 58.

Methyl 11β, - hydroxy - 16β - methyl - 3-oxo - 17α - propionyloxyandrosta - 1,4 - diene-17β - carboxylate.

A suspension of 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylic acid (250 mg.) in acetone (10 ml.) was cooled to 0° and treated with an ethereal solution of diazomethane according to Method B. After being subjected to preparative thin-layer chromatography on silica the product was crystallised from methanol to give the title methyl ester, m.p. 223—226°, $[\alpha]_D$+45.4° (*c* 0.98 dioxan), $\lambda_{max.}$ 242 nm (ε 14,820). (Found: C, 69.4; H, 7.9. $C_{25}H_{34}O_6$ requires C, 69.7: H, 8.0%).

Example 59.

t - Butyl 9α - fluoro - 11β - hydroxy - 16β-methyl - 3 - oxo - 17α - propionyloxyandrosta-1,4 - diene - 17β - carboxylate.

A suspension of 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylic acid (400 mg.) in ethyl acetate (5 ml.) was treated with O - t - butyl - N,N' - dicyclo-hexylisourea (1.14 g.) and the mixture was refluxed for 10½ hours. 2N-Hydrochloric acid was added and the mixture was stirred thoroughly; solid material was removed and washed thoroughly with ethyl acetate and water. The combined ethyl acetate solutions were washed with saturated sodium bicarbonate so'ution, and water, dried over magnesium sulphate and solvent was removed *in vacuo*. The resulting product (398 mg.) was purified by chromatography on silica and crystallised first from acetone-petrol then from methanol to give the title t-butyl ester, m.p. 200—207°, $[\alpha]_D$+35.2° (*c* 0.95, dioxan), $\lambda_{max.}$ 238—238.5 nm (ε 14,600), (Found: C, 68.8; H, 8.1. $C_{28}H_{39}FO_6$ requires C, 68.55; H, 8.0%).

Example 60.

11β,17α - Dihydroxy - 3 - oxo - androst-4 - ene - 17β - carboxylic acid.

Reaction of 11β, 17α,21 - trihydroxy-pregn - 4 - ene - 3,20 - dione (5.0 g.) with periodic acid according to Method A gave a crude product which was partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous phase was separated and acidified with dilute sulphuric acid and the resulting precipitate was collected, washed with water and dried *in vacuo*; recrystallisation from methanol gave the title acid, m.p. 235—239° (decomp.), $[\alpha]_D$+123.5 (*c* 0.57, dioxan), $\lambda_{max.}$ 241.5 nm, (ε 15,650). (Found: C, 68.4; H, 7.8. $C_{20}H_{28}O_5$ requires C, 68.9; H, 8.1%).

Example 61.

17α - Butyryloxy - 11β - hydroxy - 3-oxoandrost - 4 - ene - 17β - carboxylic acid.

11β,17α - Dihydroxy - 3 - oxoandrost - 4-ene - 17β - carboxylic acid (1.5 g.) was treated with n-butyryl chloride (3.0 ml.) and the product was solvolysed with diethylamine by the method described in Example 55 to give, after recrystallisation from methanol, 17α-butyryloxy - 11β - hydroxy - 3 - oxoandrost-4 - ene - 17β - carboxylic acid, m.p. 222—223° (decomp.) $[\alpha]_D$+45.1° (*c* 0.98, dioxan), $\lambda_{max.}$ 240 nm (ε 16,300). (Found: C, 68.3; H, 8.2. $C_{24}H_{34}O_5$ requires C, 68.9; H, 8.2%).

Example 62.

Methyl 17α - butyryloxy - 11β - hydroxy-

3 - oxoandrost - 4 - ene - 17β - carboxylate.

Treatment of 17α - butyryloxy - 11β-hydroxy - 3 - oxoandrost - 4 - ene - 17β-carboxylic acid (400 mg.) in methanol (40 ml.) with ethereal diazomethane according to method B gave, after recrystallisation from methanol, the title methyl ester, m.p. 162—165°, $[\alpha]_D$+49.4° (*c* 0.71, dioxan), $\lambda_{max.}$ 240 nm (16,550). (Found: C, 69.05; H, 8.3. $C_{32}H_{46}O_6$ requires C, 69.4; H, 8.4%).

Example 63.

11β - Hydroxy - 3 - oxo - 17α - propionyloxyandrost - 4 - ene - 17β - carboxylic acid.

Treatment of 11β,17α - dihydroxy - 3-oxoandrost - 4 - ene - 17β - carboxylic acid (3.0 g.) with propionyl chloride (2.7 ml.) and solvolysis of the product with diethylamine (3.25 ml.) by the method described in Example 55 afforded, after recrystallisation from acetone-petrol, 11β - hydroxy - 3 - oxo-17α - propionyloxyandrost - 4 - ene - 17β-carboxylic acid, m.p. 225—226° (decomp.), $[\alpha]_D$+46.2° (*c* 0.98, dioxan), $\lambda_{max.}$ 240.5 mμ (ε 15,500). (Found: C, 67.1; H, 7.8. $C_{25}H_{38}O_6 \cdot \frac{1}{2}H_2O$ requires C, 66.8; H, 7.8%).

Example 64.

Methyl 11β - hydroxy - 3 - oxo - 17α-propionyloxyandrost - 4 - ene - 17β - carboxylate.

Treatment of 11β - hydroxy - 3 - oxo - 17α-propionyloxyandrost - 4 - ene - 17β - carboxylic acid (2.5 g.) in methanol, (400 ml.) with ethereal diazomethane according to *Method B* gave a crude product; chromatography of a portion on silica afforded, after recrystallisation from methanol, the title methyl ester, m.p. 176—178° $[\alpha]_D$+51.1° (*c* 0.59, dioxan), $\lambda_{max.}$ 240 nm (ε 15,800). (Found: C, 68.9; H, 8.3. $C_{26}H_{34}O_6$ requires C, 68.9; H, 8.2%).

Example 65.

17α - Acetoxy - 11β - hydroxy - 3 - oxoandrost - 4 - ene - 17β - carboxylic acid.

Reaction of 11β,17α - dihydroxy - 3 - oxoandrost - 4 - ene - 17β - carboxylic acid (3.0 g.) with acetyl chloride (2.2 ml.) and solvolysis of the product with diethylamine (3.0 ml.) by the method described in Example 55 gave, after chromatography on silica and recrystallisation from acetone-petrol, the title 17β-carboxylic acid, m.p. 161—167°, $[\alpha]_D$+42.8° (*c* 0.25, dioxan), $\lambda_{max.}$ 241 nm (ε 14,550). (Found: C, 64.6; H, 7.5. $C_{22}H_{30}O_5$ requires C, 64.7; H, 7.9%).

Example 66.

Methyl 17α - acetoxy - 11β - hydroxy - 3-oxoandrost - 4 - ene - 17β - carboxylate.

Reaction of 17α - acetoxy - 11β - hydroxy-3 - oxoandrost - 4 - ene - 17β - carboxylic acid (2.3 g.) in methanol (368 ml.) with ethereal diazomethane according to method B gave, after recrystallisation from methanol, the title methyl ester, m.p. 250—252°, $[\alpha]_D$=+54.4° (*c* 0.61, dioxan), $\lambda_{max.}$ 240 nm (ε 15,350). (Found: C, 67.9; H, 8.0. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%).

Example 67.

2′ - Acetoxyethyl 9α - fluoro - 11β - hydroxy - 16β - methyl - 3 - oxo - 17α - propionyloxyandrosta - 1,4 - diene - 17β - carboxylate.

A solution of 2′ - hydroxyethyl 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo-17α - propionyloxyandrosta - 1,4 - diene-17β-carboxylate (300 mg.) in dry pyridine (6 ml.) was treated with acetic anhydride (0.6 ml.). After being kept at room temperature for 2½ hours the mixture was poured into well-stirred *N*-sulphuric acid to give a colourless solid (311 mg.) which was purified by preparative thin-layer chromatography on silica. Two recrystallisations from acetone afforded colourless crystals of the title acetoxyethyl ester, m.p. 156—158°, $[\alpha]_D$+31.9° (*c* 0.98, dioxan), $\lambda_{max.}$ 237 nm (ε 15,800). (Found: C, 64.6); H, 7.3. $C_{28}H_{37}FO_8$ requires C, 64.6; H, 7.2%).

The following examples (a) to (m) illustrate topical formulations prepared in accordance with the invention. In these Examples the active ingredient may be any of the active steroids hereinbefore disclosed.

The following examples (a)—(d) illustrate the preparation of ointments.

Example (a)

Active ingredient	0.1% w/w
Liquid paraffin B.P.	10.0% w/w
White soft paraffin to produce	100 parts by weight

Ball-mill the steroid with a little of the liquid paraffin until the particle size is reduced to 95% by number below 5μ. Dilute the paste and rinse out the mill with the remaining liquid paraffin, mix and add the suspension to the melted white soft paraffin at 50°C. Stir until cold to give a homogeneous ointment.

Example (b)

Active ingredient	0.25% w/w
Aluminium stearate	3.2% w/w
Liquid paraffin B.P. to	100 parts

Disperse the aluminium stearate in the liquid paraffin by vortex stirring and heat the suspension with continued stirring, at a temperature rise of 2°C per minute until 90°C is reached. Maintain the temperature at 90—95°C for 30 minutes until solution is complete and a gel is formed. Cool quickly, preferably by the use of cooling coils or concentric cooling rings to produce a transparent solid gel.

Mill the active ingredient to produce microfine particles of which not less than 90% by number are below 5μ. Triturate with a small portion of the gel and incorporate the remaining gel to give a homogeneous mix.

Example (c)

Active ingredient	0.1% w/w
Woolfat	12.0% w/w
Cetostearyl alcohol B.P.C.	20.0% w/w
Liquid paraffin B.P.	25.0% w/w
White soft paraffin to	100 parts w/w

Ball-mill the steroid with a little of the liquid paraffin as in Example (a) and add the resulting paste, diluted with the remaining liquid paraffin, to a mixture of cetostearyl alcohol, woolfat and white soft paraffin, melted together by gentle warming. Stir until cold to give a homogeneous mix.

Example (d)

Active ingredient	0.05% w/w
Hydrogenated lanolin e.g. Lanocerina sold by Croda Ltd. of London, W.C.2. England.	20.0% w/w
Liquid paraffin B.P.	15.0% w/w
White soft paraffin to	100 parts w/w

Ball-mill the steroid with liquid paraffin as in Example (a), and add the resulting paste, diluted with the remaining liquid paraffin, to the mixture of hydrogenated lanolin and white soft paraffin melted together by gently warming. Stir until cold to give a homogeneous mix.

The following examples (e) and (f) illustrate the preparation of water-miscible creams:—

Example (e)

Active ingredient	0.1% w/w
Beeswax (White)	15.0% w/w
Cetostearyl alcohol B.P.C.	7.0% w/w
Cetomacrogel 1000 B.P.C.	3.0% w/w
Liquid paraffin B.P.	5.0% w/w
Chlorocresol	0.1% w/w
Distilled water to produce	100 parts by weight

Ball-mill the steroid with a little liquid paraffin as described in Example (a). Heat the available water to 100°C, add the chlorocresol, stir to dissolve and cool to 65°C. Melt together the beeswax, cetostearyl alcohol and cetomacrogel and maintain at 65°C. Add the steroid suspension using the remaining liquid paraffin for rinsing. Add the steroid oil phase at 60°C to the chlorocresol aqueous phase at 65°C and stir rapidly while the emulsion cools over the gelling point (40—45°C). Continue to stir at slow speed until the cream sets.

Example (f)

Active ingredient	0.1% w/w
Cetostearyl alcohol B.P.C.	7.2% w/w
Cetomacrogel 1000 B.P.C.	1.8% w/w
Liquir paraffin B.P.	6.0% w/w
White soft paraffin	15.0% w/w
Chlorocresol	0.1% w/w
Distilled water to produce	100 parts by weight

Prepare as described in Example (e), replacing the beeswax with white soft paraffin in the oily phase.

The following examples (g) and (h) illustrate the preparation of lotions:

Example (g)

Active ingredient	0.25% w/v
Lanbritol wax* (the word "Lanbritol" is a registered Trade Mark)	0.93% w/v
Diethylene glycol monostearate	0.65% w/v
Cetostearyl alcohol B.P.C.	0.65% w/v
Liquid paraffin B.P.	1.95% w/v
Glycerin	5.0% v/v
Isopropyl alcohol	6.5% v/v
Methyl *p*-hydroxy benzoate	0.15% w/v
Distilled water to produce	100 volumes

Ball-mill the steroid with half the glycerin, as in Example (a), and use the isopropyl alcohol for dilution and rinsing purposes.

Melt together the lanbritol wax, diethylene glycol monostearate, cetostearyl alcohol and liquid paraffin and maintain at 60°C. Heat the available water and remaining glycerin to 95°C. Add the methyl parahydroxy benzoate and stir until dissolved. Cool to 65°C. Add the oily mix at 60°C to the aqueous phase at 65°C and allow to cool while stirring rapidly until the emulsion gels at 40—45°C, and thereafter stir slowly. Add the well mixed steroid suspension slowly to the lotion base and stir to obtain a homogeneous mix.

*Lanbritol wax is a non-ionic wax for stabilising emulsions consisting of a mixture of fatty alcohols with polyethylene glycol ethers of fatty alcohols sold by Ronsheim Moore of London W.C.1 England.

Example (h)

Active ingredient	0.05% w/v
Tween 80 (the word "Tween" is a registered Trade Mark)	
(Polyoxyethylene sorbitan mono-oleate)	0.01% w/v
Carbopol 934 (the word "Carbopol" is a registered Trade Mark)	
(Carboxy vinyl polymers)	0.3% w/v
Diethanolamine	0.5% w/v (approx.)
Distilled water to produce	100 volumes.

Ball-mill the steroid with a little water and the Tween 80 as in Example (a). Disperse the Carbopol 934 in the available water by vortex stirring. Add the diethanolamine slowly with stirring until the clear thickened mix has a pH of 7.0. Incorporate the steroid slurry into the lotion base and mix well.

Example (i)

Aerosol Spray Lotion

Active ingredient (microfine)	2.5 mgm.
Fractionated coconut oil to	1.20 g.
Dichlorodifluoromethane	16.32 g.
Trichlorofluoromethane	24.48 g.

Dry the steroid overnight at 60°C under vacuum and over phosphorus pentoxide. Ball-mill the dried powder for at least 4 hours with a little of the dried filtered oil. Rinse out the mill with more dried filtered oil and pass the suspension through a 325 mesh B.S. sieve. Assay the suspension and dilute with more dried filtered oil to the required concentration. Incorporate the suspension into the pressure container with the propellants in a conventional manner.

Example (j)

Aphthous Ulcer Pellets

Active ingredient (microfine)	0.25 mg.
Lactose	69.90 mg.
Acacia	3.00 mg.
Magnesium stearate	0.75 mg.

Pass the steroid, lactose and acacia separately through a No. 60 B.S. mesh sieve. Blend the powders and granulate with 50% ethanol in water. Pass the mass through a No. 12 mesh sieve and dry the granules at 50°C. Pass the dried granules through a No. 20 mesh B.S. sieve and blend in the magnesium stearate, previously passed through a No. 100 mesh B.S. sieve. Compress in a conventional manner on 7/32 inch diameter punches, to give a pellet that will dissolve slowly in the mouth.

Example (k)

Retention Enema

Active ingredient (microfine)	0.0005% w/v
Tween 80	0.05% w/v
Ethanol	0.015% v/v
Methyl *p*-hyd. oxy benzoate	0.08% w/v
Propyl *p*-hydroxy benzoate	0.02% w/v
Distilled water to	100 vols.

Heat the available water to 95°C, add the methyl and propyl *p*-hydroxy benzoates and stir to dissolve. Cool the vehicle to room temperature. Disperse the steroid in the ethanol and add to the Tween 80; warm the mixture to 50°C and stir until the steroid is in solution. Add the steroid solution to the vehicle, stirring vigorously to avoid precipitation, and make up to volume with water if required. Distribute the enema into plastic bags e.g. P.V.C., bags for self-administration or into other containers suitable for use.

Example (l)

Eye Drops

Active ingredient	0.025% w/v
Tween 80	2.5% w/v
Ethanol	0.75% w/v
Benzalkonium chloride	0.02% w/v
Phenyl ethanol	0.25% v/v
Sodium chloride	0.60% w/v
Water for injection to	100 volumes.

Dissolve the sodium chloride, benzalkonium chloride and phenyl ethanol in the water for injection. Suspend the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until dissolved. Add the steroid solution to the eye-drop vehicle with rapid stirring to obtain a clear solution. Sterilise the bulk by filtration through a sintered glass filter and distribute into sterile small neutral glass eye-drop containers.

Example (m)

Nasal Drops

Active ingredient	0.005% w/v
Tween 80	0.05% w/v
Alcohol 95%	0.15% v/v
Methyl paraben (*p*-hydroxy benzoate)	0.04% w/v
Propyl paraben (*p*-hydroxy benzoate)	0.02% w/v
Sodium chloride	0.70% w/v
Distilled water to	100 volumes

Dissolve the sodium chloride and the parabens in the distilled water heated to 95°C, and allow the solution to cool. Disperse the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until solution of the steroid is effected. Add the steroid solution to the vehicle with rapid stirring to obtain a clear solution. Filter the solution free from particulate matter through a sintered glass filter and distribute into small, well filled containers.

The following Examples (n) and (o) illustrate formulations for internal administration according to the invention. In both Examples the active ingredient used may be any of the active steroid hereinbefore disclosed.

Example (n)

Oral Tablet

Active ingredient	0.5 mg.
Lactose	175.5 mg.
Maize starch (dried)	20.0 mg.
Gelatin	2.0 mg.
Magnesium stearate	2.0 mg.
Total weight	200.0 mg.

A suspension of 300 mg. of the active ingredient in 2 ml. of water containing 0.1% of Tween 80 was milled for 16 hours in a 10 ml. nylon pot about three quarters filled with steatite balls, until 90% by number of the particles had a diameter of less than 10 microns. The maize starch and lactose were blended and passed through a 60 mesh B.S. sieve and granulated with a 10% solution of gelatin, containing the suspension of the active ingredient and washings from the nylon pot, by passing through a 16 mesh B.S. sieve. The granules were dried at 40°C overnight, passed through a 20 mesh B.S. sieve and blended with magnesium stearate and tabletted using a tabletting machine having a 5/32 inch flat-bevelled punch.

Example (o)

Intra-Articular Injection

a) Preparation of small particle active ingredient.

2.8 g. Tween 80 was dissolved in 130 ml. of dimethyl acetamide (DMA). 12 g of the active ingredient was then dissolved in 130 ml. of this solution and the resulting solution was filtered successively through two dry sintered glass filters (No. 3 and No. 4).

The solution of active ingredient was then added, under aseptic conditions, in a fine stream to a stirred sterile aqueous solution of benzyl alcohol (10 g. in 1 litre water) over a period of ten minutes. The preparation was allowed to stand for at least three hours and the resulting crystals collected by filtration or centrifuging. The preparation was washed with aqueous benzyl alcohol (10 g. in 1 litre water) and the wet-cake transferred to a well-sealed container. 90% by number of the particles had a diameter less than 10μ and none were above 50μ in diameter.

b) Production of Injectable Preparation

Composition:	% w/v
Fine particle ingredient prepared as in a)	0.50
Hydroxyethyl cellulose	0.40
Benzyl alcohol	1.00
Sodium citrate	0.30
Sodium salt of EDTA*	0.01
Sodium chloride	0.44
Citric acid	q.s.
Water for injection to pH value 4.80 to 5.50	100.0

*EDTA is ethylene diamine tetracetic acid.

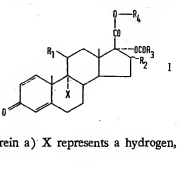
1. *Vehicle*

The hydroxyethyl cellulose was dissolved in 17.5 litres of Water for Injection using a high speed vortex stirrer. The benzyl alcohol was added with stirring. The sodium chloride and sodium citrate salt of EDTA were dissolved in 1 litre of water and added to the bulk vehicle with stirring. The pH value of the bulk vehicle was adjusted to 4.80 to 5.50 with a solution of citric acid. The volume was then adjusted to 19.3 litres and the vehicle clarified by filtration through nylon. The vehicle was finally sterilised by autoclaving.

2. Sterile wet-cake of small particle ingredient prepared as in a) containing 100 g. of the active ingredient was added with stirring and under aseptic conditions to 19 litres of the vehicle, and the volume made up to 20 litres. The resulting suspension was passed through a sterile 100 mesh British Standard sieve and stored in a sealed container. Dosage units for injection were prepared by aseptically filling neutral glass ampoules or vials closed by a pure latex plug.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein a) X represents a hydrogen, chlorine

or fluorine atom; R_1 represents a hydroxy group in the β-configuration or (when X represents a chlorine atom) R_1 may also represent a chlorine atom in the β-configuration; R_2 represents a hydrogen atom, a methylene group or a methyl group (in either the α- or β-configuration); R_3 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or a phenyl group; R_4 represents a C_{1-4} alkyl group; a C_{1-4} alkyl group substituted by either at least one halogen or an alkoxycarbonyl group wherein the alkoxy moiety contains 1 to 4 carbon atoms; or a (C_{2-4}) alkyl group substituted by a C_{2-5} alkanoyloxy group; and ——— represents a single or double bond; provided that R_1 is not propyl, isopropyl or n-butyl unless one or more of X, R_2 and R_3 is other than hydrogen and/or ——— represents a double bond; or b) X represents a chlorine or fluorine atom; R_1 represents an oxo group; R_2 represents a hydrogen atom, a methylene group or a methyl group (in either the α- or β-configuration); R_3 represents a methyl or ethyl group; R_4 represents a C_{1-4} alkyl group; a C_{1-4} alkyl group substituted by either at least one halogen atom or an alkoxycarbonyl group wherein the alkoxy moiety contains 1 to 4 carbon atoms; or a C_{2-4}) alkyl group substituted by a C_{2-5} alkanoyloxy group; and ——— represents a single or double bond.

2. Compounds as claimed in claim 1 wherein R_3 represents an alkyl group containing 1 to 3 carbon atoms, a phenyl group or (when R_2 is a methylene or methyl group) a hydrogen atom.

3. Compounds as claimed in claim 1 wherein R_3 represents a methyl, ethyl, n-propyl or iso-propyl group.

4. Compounds as claimed in claim 1 wherein R_3 represents a hydrogen atom and R_4 represents a methyl group.

5. Compounds as claimed in any of the preceding claims wherein R_4 represents a C_{1-4} alkyl group.

6. Compounds as claimed in claim 5 wherein R_4 represents a methyl group.

7. Compounds as claimed in claim 5 wherein R_4 represents an ethyl or propyl group.

8. Compounds as claimed in claim 1 wherein R_4 represents a C_{1-4} alkyl group substituted by a chlorine, fluorine or bromine atom.

9. Compounds as claimed in claim 1 wherein R_4 represents (C_{2-4}) alkyl group substituted by an acetoxy group.

10. Compounds as claimed in claim 1 wherein the C_{1-4} alkyl group is substituted by a methoxycarbonyl group.

11. Compounds as claimed in any of the preceding claims wherein R_2 represents a methyl group in the β-configuration.

12. Compounds as claimed in claim 1 wherein X represents a chlorine or fluorine atom, R_1 represents a β-hydroxy group, R_2 represents a methyl group, R_3 represents a methyl, ethyl or n-propyl group, R_4 represents a methyl group and ——— represents a double bond.

13. Compounds as claimed in claim 12 wherein X represents a fluorine atom and R_2 represents a methyl group in the β-configuration.

14. Compounds as claimed in claim 1 wherein X represents a fluorine atom, R_1 represents a keto group, R_2 represents a methyl group in the β-configuration, R_3 represents a methyl or ethyl group, R_4 represents a methyl group and ——— represents a double bond.

15. Compounds as claimed in claim 1 wherein X represents a fluorine or chlorine atom, R_1 represents a β-hydroxy group, R_2 represents a methylene group, R_3 represents a methyl, ethyl, n-propyl or iso-propyl group and R_4 represents a methyl or ethyl group.

16. Compounds as claimed in claim 15 wherein X represents a fluorine atom, R_1 represents a methyl group and ——— represents a double bond.

17. Compounds as claimed in claim 1 wherein ——— represents a single bond, X represents a fluorine or chlorine atom, R_1 represents a β-hydroxy group, R_2 represents a methyl group, R_3 represents a methyl, ethyl or n-propyl group and R_4 represents a methyl or ethyl group.

18. Compounds as claimed in claim 17 wherein X represents a fluorine atom, R_2 represents a methyl group in the β-configuration and R_4 represents a methyl group.

19. Compounds as claimed in claim 1 wherein X represents a hydrogen atom, R_1 represents a β-hydroxy group and R_2 represents a hydrogen atom or a methyl group.

20. Compounds as claimed in claim 19 wherein R_2 represents a methyl group in the β-configuration.

21. Compounds as claimed in claim 19 or claim 20 wherein R_3 represents an alkyl group containing 1, 2 or 3 carbon atoms.

22. Compounds as claimed in claim 21 wherein R_3 represents an alkyl group containing 2 carbon atoms.

23. Compounds as claimed in any of claims 19 to 22 wherein R_4 represents a C_{1-4} alkyl group.

24. Compounds as claimed in claim 23 wherein R_4 represents a methyl group.

25. Compounds as claimed in any of claims 19 to 24 wherein ——— represents a double bond.

26. Compounds as claimed in claim 1 wherein X and R_1 represent chlorine atoms, R_2 represents a methyl group, R_3 represents a methyl or ethyl group, R_4 represents a methyl or ethyl group and ——— represents a double bond.

27. Compounds as claimed in claim 26 wherein R_2 represents a methyl group in the α-configuration.

28. Methyl 17α - acetoxy - 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

29. Methyl 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate.

30. Methyl 17α - butyryloxy - 9α - fluoro-11β - hydroxy - 16β - methyl - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

31. Methyl 17α - acetoxy - 9α - fluoro-11β - hydroxy - 16α - methyl - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

32. Methyl 9α - fluoro - 11β - hydroxy-16α - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate.

33. Methyl 17α - butyryloxy - 9α - fluoro-11β - hydroxy - 16α - methyl - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

34. Methyl 9α - fluoro - 11β - hydroxy-16 - methylene - 3 - oxo - 17α - propionyl-oxy - androsta - 1,4 - diene 17β - carboxylate.

35. Methyl 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androst - 4 - ene - 17β -carboxylate.

36. Methyl 17α -acetoxy - 9α - fluoro-16β - methyl - 3,11 - dioxoandrosta - 1,4-diene - 17β - carboxylate.

37. Ethyl 9α - fluoro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate.

38. Methyl 17α - acetoxy - 9α,11β - dichloro - 16α - methyl - 3 - oxo - androsta-1,4 - diene - 17β - carboxylate.

39. Methyl 9α - fluoro - 11β - hydroxy-17α - isobuyryloxy - 16 - methylene - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

40. Ethyl 9α - flloro - 11β - hydroxy - 17α-isobutyryloxy - 16 - methylene - 3 - oxo-androsta - 1,4 - diene - 17β - carboxylate.

41. Methyl 11β - hydroxy - 16β - methyl-3 - oxo - 17α - propionyloxyandrosta - 1,4-diene - 17β - carboxylate.

42. Methyl 11β - hydroxy - 3 - oxo - 17α-propionyloxyandrost - 4 - ene - 17β - carboxylate.

43. Methyl 9α - chloro - 11β - hydroxy-16β - methyl - 3 - oxo - 17α - propionyloxy-androsta - 1,4 - diene - 17β - carboxylate.

44. A process for the preparation of compounds of formula I (as defined in claim 1) which comprises esterifying a corresponding 17α - monoester 17β - carboxylic acid (or functional equivalent thereof) or 17α-hydroxy 17β-carboxylate to produce the desired compound of formula I.

45. A process as claimed in claim 44 wherein the 17α-monoester 17β-carboxylic acid is esterified with a diazoalkane.

46. A process as claimed in claim 45 wherein the said diazoalkane is diazomethane.

47. A process as claimed in claim 45 or claim 46 wherein the esterification is effected in a solvent medium.

48. A process as claimed in any of claims 45 to 47 wherein the esterification is effected at a temperature of −5 to +30°C.

9. A process as claimed in claim 44 wherein the 17α-monoester 17β-carboxylic acid is esterified with an O-alkyl-N,N'-dicyclohexyl-isourea.

50. A process as claimed in claim 44 wherein a salt of the 17α-monoester 17β-carboxylic acid is reacted with an alkyl halide or dialkyl sulphate to effect esterification.

51. A process is claimed in claim 50 wherein the said salt is an alkali metal or quaternary ammonium salt.

52. A process as claimed in claim 50 wherein the said salt is a lithium, sodium, potassium, triethylammonium or tetrabutyl-ammonium salt.

53. A process as claimed in any of claims 50 to 52 wherein the said salt is reacted with an alkyl iodide.

54. A process as claimed in any of claims 50 to 52 wherein the said salt is reacted with dimethyl sulphate.

55. A process as claimed in any of claims 50 to 54 wherein the reaction is effected in a polar solvent medium.

56. A process as claimed in any of claims 50 to 55 wherein the reaction is effected at a temperature of 25 to 100°C.

57. A process as claimed in claim 44 wherein the 17α-hydroxy 17β-carboxylate is reacted with an appropriate carboxylic acid.

58. A process as claimed in claim 57 wherein the reaction is effected in the presence of trifluoroacetic anhydride.

59. A process as claimed in claim 57 or claim 58 wherein the reaction is effected in the presence of an acid catalyst.

60. A process as claimed in claim 59 wherein the acid is p-toluene-sulphonic acid or sulphosalicylic acid.

61. A process as claimed in any of claims 57 to 60 wherein the reaction is effected in an organic solvent medium.

62. A process as claimed in any of claims 57 to 61 wherein the reaction is effected at a temperature of 20—100°C.

63. A process as claimed in claim 44 wherein the 17α - hydroxy 17β - carboxylate is reacted with the acid anhydride or chloride of an appropriate carboxylic acid.

64. A process as claimed in claim 63 wherein the reaction is effected in a non-hydroxylic solvent.

65. A process as claimed in claim 63 or claim 64 wherein the reaction is effected in the presence of a strong acid or a strongly acidic cation exchange resin.

66. A process for the preparation of compounds of formula I (wherein R_1 represents an oxo group) which comprises oxidising a corresponding compound of formula I wherein R_1 represents a β-hydroxy group.

67. A process as claimed in claim 66 where-

in the oxidation is effected by means of chromium trioxide.

68. A process for the preparation of compounds of formula I (wherein ——— represents a single bond) which comprises partially reducing a corresponding compound of formula I (wherein ——— represents a double bond) to produce the desired Δ^4 compound.

69. A process as claimed in claim 68 wherein the partial reduction is effected by hydrogenation with a palladium catalyst.

70. A process as claimed in claim 68 wherein the partial reduction is effected by homogeneous hydrogenation using tris-(triphenylphosphine) rhodium chloride.

71. A process as claimed in claim 68 wherein the partial reduction is effected by exchange hydrogenation with cyclohexene in the presence of a palladium catalyst.

72. A process for the preparation of compounds of formula I (wherein R_1 represents a C_{1-4} alkyl group substituted by either a halogen atom or a C_{2-5} alkoxycarbonyl group or a C_{2-5} alkyl group substituted by a C_{2-5} alkanoyloxy group) which comprises reacting a salt of the parent 17β-carboxylic acid with an appropriate halo compound serving to introduce the desired group R_4 in the compound of formula I.

73. A process as claimed in claim 72 wherein the salt of the parent 17β-carboxylic acid is an alkali metal salt or a quaternary ammonium salt.

74. A process as claimed in claim 73 wherein the said salt is a lithium, sodium, potassium, triethylammonium or tetrabutylammonium salt.

75. A process for the preparation of compounds of formula I wherein R_4 represents a C_{2-5} alkyl group substituted by a C_{2-5} alkanoyloxy group which comprises acylating a corresponding hydroxy-substituted compound to introduce the desired acyl group.

76. A process for the preparation of compounds of formula I wherein R_4 represents a C_{1-4} alkyl group substituted by a methoxy carbonyl group which comprises reacting a corresponding compound of formula I (wherein R_4 represents a C_{1-4} alkyl group substituted by an ethoxycarbonyl group) with methanol in the presence of an acid catalyst.

77. A process for the preparation of compounds of formula I wherein R_4 represents a C_{2-5} alkyl group substituted by at least one halogen atom (other than in the α-position) which comprises sulphonating the corresponding hydroxy substituted compound of formula I to form the corresponding sulphonyloxyalkyl 17β-carboxylate compound which is subsequently halogenated to form the corresponding desired halo-compound.

78. A process for the preparation of compounds of formula I wherein R_4 represents a C_{1-4} alkyl group substituted by a halogen atom at the carbon atom attached to the oxygen atom of the 17β-carboxylate function, which process comprises reacting the parent 17β-carboxylic acid with an appropriate aldehyde in the presence of a hydrohalic acid.

79. A process as claimed in any of claims 44 to 65 wherein the 17α-monoester 17β-carboxylic acid or 17α-hydroxy 17β-carboxylate employed as starting material is prepared by oxidising a corresponding pregnane compound having the following partial formula at the 17-position.

[wherein R represents a hydrogen atom or group of formula —COR_5 (wherein R_5 is as defined in claim 1)] and (when R represents a hydrogen atom) esterifying the 17β-carboxyl group of the resulting 17α-hydroxy 17β-carboxylic acid to produce the said 17α-hydroxy 17β-carboxylate.

80. A process as claimed in claim 79 wherein the said pregnane compound is oxidised by means of periodic acid.

81. A process as claimed in claim 80 wherein the oxidation is effected in a solvent medium.

82. A process as claimed in claim 79 wherein the said pregnane compound (wherein R represents a group of formula —COR_5) is oxidised with sodium bismuthate.

83. A process as claimed in any of claims 79 to 81 wherein the esterification of the 17β-carboxyl group is effected by means of an appropriate diazoalkane or by reaction of a salt of the 17β-carboxylic acid with an appropriate alkylating agent.

84. A process as claimed in any of claims 44 to 65 wherein the 17α-monoester 17β-carboxylic acid employed as starting material is prepared by esterifying the corresponding 17α-hydroxy 17β-carboxylic acid with an appropriate carboxylic acid anhydride to give the 17α-monoester of the mixed anhydride of the 17β-carboxylic acid and the carboxylic acid of the starting anhydride, the resulting anhydride being solvolysed to produce the desired 17β-carboxylic acid.

85. A process as claimed in any of claims 44 to 65 wherein the 17α-monoester 17β-carboxylic acid employed as starting material is prepared by esterifying the corresponding 17α-hydroxy 17β-carboxylic acid with an appropriate carboxylic acid chloride.

86. A process for the preparation of compounds of formula I (as defined in claim 1), substantially as herein described.

87. A process for the preparation and androstane compounds substantially as herein described with reference to any of the Ex-

amples 1 to 67 (with the exception of Examples 1, 17, 23, 34, 50, 53, 56 and 60).

88. Compounds of formula I whenever prepared by a process as claimed in any of claims 44 to 87.

89. Pharmaceutical compositions comprising at least one compound of formula I (as defined in claim 1) together with one or more pharmaceutical carriers or excipients.

90. Pharmaceutical compositions for use in the topical treatment of inflammations comprising at least one compound of formula I (as defined in claim 1) together with a topical vehicle for said compound.

91. Compositions as claimed in claim 90 in the form of lotions, powders, drops, sprays, suppositories, retention enemas, chewable or suckable tablets or pellets, aerosols, ointments or creams.

92. Compositions as claimed in either of Claims 89 or 90 containing from 0.001 to 5% by weight of said compound.

93. Compositions as claimed in claim 92 containing from 0.001 to 0.5% by weight of said compound.

94. Compositions as claimed in claim 92 containing from 0.01 to 0.25% by weight of said compound.

95. Compositions as claimed in claim 89 comprising a compound of formula I (as defined in claim 1) in association with a vehicle therefor adapted for internal administration.

96. Compositions as claimed in claim 95 in dosage unit form, each dosage unit containing from 0.05 to 2.0 mg of said compound.

97. Compositions as claimed in claim 96 in which each dosage unit contains from 0.25 to 1.0 mg of said compound.

98. Compositions as claimed in claim 96 or 97 in the form of tablets, coated tablets, capsules, ampoules or vials for parenteral administration, suppositories or sterile tablet or pellet implants.

99. Compositions as claimed in claim 95 comprising said compound dissolved or dispersed in a sterile aqueous or oily vehicle for parenteral administration.

100. Compositions as claimed in any of claims 95 to 99 containing from 0.01 to 5.0% of said compound.

101. Compositions as claimed in any of claims 89 to 100 also including an antimicrobial agent.

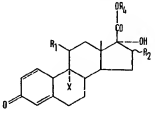
102. Compositions as claimed in any of claims 89 to 101 in which the compound of formula I is a compound as claimed in any of claims 2—40.

103. Compositions as claimed in any of claims 89 to 101 in which the compound of formula I is a compound as claimed in any of claims 41—43.

104. Pharmaceutical compositions as claimed in claim 89 substantially as herein described.

105. Pharmaceutical compositions as claimed in claim 89 substantially as herein described with reference to any of Examples (a) to (o).

106. Compounds of general formula

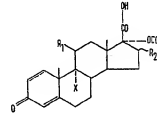


(wherein R_1, R_2, R_4, X and ==== are as defined in claim 1) providing that when R_4 represents a β-hydroxy group, R_2 and X both represent hydrogen atoms and ==== represents a single bond, R_4 does not represent a C_{1-4} alkyl group.

107. Compounds as claimed in claim 106 wherein R_2 represents a methyl or methylene group.

108. Compounds as claimed in claim 106 or claim 107 wherein X represents a chlorine or fluorine atom.

109. Compounds of general formula



(wherein R_1, R_2, R_3, X and ==== are as defined in claim 1) and their carboxylic acid anhydrides.

110. 2′ - Hydroxyethyl 9α - fluoro - 11β-hydroxy - 16β - methyl - 3 - oxo - 17α-propionyloxy - androsta - 1,4 - diene - 17β-carboxylate.

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